

## CORRESPONDENCE

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### Diagnosis of Pancreatic Cystic Neoplasms: A Report of the Cooperative Pancreatic Cyst Study

Dear Sir:

I would like to commend Brugge et al on their recent study,<sup>1</sup> which addresses the utility of endoscopic ultrasonography (EUS) and EUS coupled with fine needle aspirate (EUS-FNA) in the diagnosis of cystic neoplasms of the pancreas. However, I would like to raise my concern about the conclusions of this paper, which implies that the analysis of cyst fluid carcinoembryonic antigen (CEA) concentration via EUS-FNA is accurate and should be performed in the evaluation of a pancreatic cyst. In their study, EUS morphology, cytology, or CEA were reported to have specificities and sensitivities of 45.4% and 56.1%, 83.3% and 34.5%, or 83.6% and 75%.

When all 3 EUS criteria were used, the sensitivity increased to 91% but specificity decreased to only 31%. Thus, I interpret this study as demonstrating the poor utility of EUS-FNA in the preoperative diagnosis of pancreatic cystic neoplasms. Based on the results of this study, I question the value of performing a preoperative EUS-FNA for the diagnosis of pancreatic cystic neoplasms. With the low morbidity and mortality rates currently achievable with pancreatic resections,<sup>2</sup> a patient would probably be better off if the cystic lesion is surgically removed from the onset than having the cyst fluid CEA analyzed preoperatively via EUS-FNA as approximately 16% nonmucinous lesions would be missed and wrongly managed conservatively.

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### Is Somatosensory Cortex Activated During Proximal Stomach Stimulation and the Role of Insula in Visceral Pain

Dear Sir:

We have read with interest the recently published study by Vandenberghe et al,<sup>1</sup> reporting a constellation of regional brain activation during gastric fundus distention (GFD) by positron emission tomography (PET). Significant activation was noted in the superior temporal gyrus (BA 38), inferior frontal gyrus (BA 47) and anterior cingulate gyrus (BA24), as well as anterior insula and cerebellar hemispheres. Most of the engaged neuronal substrates were in

agreement with our recent fMRI study.<sup>2</sup> Both studies also showed a progressive increase of brain activation magnitude with increasing distending pressure, suggesting of no distinct neuronal networks in processing noxious (pain) and innocuous (fullness) GFD. However, several differences between these 2 studies may merit further discussion.

SI and SII are thought to be the 2 key substrates of the lateral pain system that encodes the spatial localization and intensity discrimination of the somatic sensation.<sup>3</sup> The role of somatosensory cortex (SI/SII) in the processing of visceral pain is still under debate. Vandenberghe et al reported a pronounced activation of the lateral pain system (SI/SII).<sup>1</sup> On the contrary, neither SI nor SII were activated during both full and painful GFD in our fMRI study, which is corroborated by 2 recent PET studies with noxious distal and non-noxious proximal stomach balloon distention.<sup>4,5</sup> We suggested that the lack of activation in SI/SII in gastric stimulation may account for the ambiguous nature of the visceral pain. In a recent meta-analysis of functional brain imaging studies involving visceral pain in esophagus and anorectum, SI/SII were activated in the majority of reports.<sup>6</sup> Furthermore, esophagus stimulation will have greater involvement of sensory (SI/SII), while anorectal stimulation will result in more activation in the affective process. Because of the intermediate anatomical position of the proximal stomach, Vandenberghe et al suggests that the brain activation pattern in the proximal stomach is a mixture of both esophagus and anorectum.<sup>1</sup> However, the esophagus and anorectum are the only 2 segments in the whole GI tract having a somatic component, thus it is not surprising to have SI/SII activation with either area being stimulated. Therefore, it seems unusual to have SI/SII activation after stomach stimulation. In the somatic pain model, however, the intensity and type of stimulation, the varied cognitive modulation in each experimental setting, the variation of SI sulcal anatomy across subjects, and different analytic approaches will all account for the presence or absence of SI/II activation in PET or fMRI.<sup>7</sup> Hence, more studies are needed to clarify this important issue in visceral pain.

Insula is the key region which is activated in almost all of the functional brain imaging studies involving visceral pain, and this finding resonates with the description by Craig of insula as a visceral sensory area.<sup>8</sup> We, in our fMRI study, further reported that the activated loci of gastric representation in the insula were clustered in a position higher than other parts of the gut (average coordinate of z axis in right insula: esophagus = -4, anorectum = 0; stomach = 6).<sup>2</sup> The results suggest the possibility of a viscerotopical organization in the insula of humans, which already exists in rats.<sup>9</sup> On the contrary, Vandenberghe et al<sup>1</sup> reported a lower level (-2) in the maximal coordinate at right anterior insula in z axis when compared with our and the Ladabaum's study.<sup>2,4</sup> Therefore, a function brain image study concurrently simulating various parts of the gastrointestinal tract is heuristic to verify or dispute a viscerotopical organization in human insula.

In conclusion, the current 2 functional brain image studies coherently show that gastric pain induced by GFD is represented in the paralimbic and limbic structures, in addition to many other parts of the brain. The constellations of activation overlap substantially those

pain matrices as disclosed by experimentally induced musculoskeletal<sup>10</sup> and other types of visceral pain. More studies are needed to clarify the role of SI/SII in processing visceral pain and the possible existence of a viscerotopical organization in the human insula.

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**Reply.** We have read with interest the letter by Lu et al<sup>1</sup> concerning the similarities and differences between our recent PET study and their recent fMRI study on regional brain activation during proximal stomach distention.<sup>2,3</sup> Unfortunately, we were not able to cite the interesting and well-conducted study by Lu et al or compare their results to ours because it was published after submission of our article.

Several neuronal structures were indeed found to be activated by proximal stomach distention in both studies, which certainly contributes to the identification of the “neuromatrix” involved in the processing of gastric sensation and pain. Moreover, most of the findings are in line with other studies investigating the neurological substrates of gastrointestinal or, more specifically, gastric distention.<sup>4,5</sup> Especially the role of the insula as “interoceptive cortex,”

processing visceral sensory information as well as visceral and somatic pain, has clearly been established.<sup>4,6–8</sup> The question regarding viscerotopic organization of the human insula certainly merits further research, and we agree that the data by Lu et al<sup>1</sup> provide some support for this hypothesis. However, given the different resolution and sensitivity of PET and fMRI and the results of our study,<sup>2</sup> we believe it may be difficult to draw vast conclusions based on comparison of functional imaging studies alone. Therefore, we agree with Lu et al<sup>1</sup> that a functional brain imaging study stimulating various parts of the gastrointestinal tract in the same series of volunteers could be helpful to provide further evidence.

We also agree with the fact that the role of somatosensory cortices (SI/SII) in the processing of visceral sensation or pain and even somatic pain remains a matter of controversy. However, some important differences between both studies that have not been addressed so far could account for the differential activation of SI/SII. Furthermore, there is a considerable body of evidence supporting a potential role for SI/SII in the processing of visceral sensation or pain. Firstly, there is an important gender difference between both studies. Lu et al studied a population of volunteers, which was predominantly male (80% men), whereas our volunteers were predominantly female (55% women). This may be an important issue, as sex differences in processing of visceral and somatic sensation and pain have been reported.<sup>9,10</sup>

Secondly, the distending stimulus is not identical in both studies. The diameter and volume of the balloon used are similar, as well as the distending pressure to induce fullness and gastric pain. The duration of the distentions, (40 seconds in the study by Lu et al, 2 minutes in our study) and the distention protocol though, are different. This may provide one of the possible explanations for the differential activation in SI/SII in both studies. Somatosensory cortex is believed to be important in intensity coding and temporal summation is suggested as a determinant of SI activation in the somatic pain literature.<sup>7</sup> Thirdly, differences in attention toward the stimulus, anticipation or anxiety between the two studies could be important.<sup>7</sup>

Furthermore, Craig’s view on visceral sensation and pain,<sup>8</sup> does not exclude a role for somatosensory cortex, as he clearly states that multimodal wide-dynamic range neurons in lamina V of the dorsal horn receive visceral and noxious stimuli-related input and project via the thalamus (VPL) to somatosensory cortex,<sup>8</sup> and there is growing evidence that this pathway plays an important role in the processing of both somatic and visceral pain.<sup>11–13</sup> Thus, the difference between interoception (insula) and exteroception (SI/SII) may not be as clear as in Craig’s view.<sup>12</sup> For example, Strigo et al<sup>11</sup> found activation of SI during visceral but not during somatic noxious stimulation. Furthermore, Craig clearly states that the unimodal “labeled lines” originating from lamina I project not only to the insula via the thalamus (VMpo), but also to a specific subregion within SI (area 3a) via the same thalamic nucleus.<sup>8</sup> Both these projections could account for activation of somatosensory cortex found in our study.

In their letter, Lu et al also suggest that the “somatic component” involved in stimulation of the esophagus and anorectum could explain the activation of SI/SII in studies stimulating these 2 regions. However, in all studies on esophageal sensation and pain,<sup>11,14,15</sup> the distal and not the proximal esophagus was stimulated, which makes involvement of a somatic component less likely. The same argument holds for rectal distention as the rectum is usually stimulated far enough from the anal sphincter to exclude a somatic component.

Finally, interindividual variations in the anatomy of the complex frontoparietal opercular, perisylvian, and perirolandic regions exist and SII is not clearly defined in humans. Together with the resolution